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THE PHYSIOLOGICAL BEHAVIOR OF RUBIDIUM AND CESIUM IN RELATION TO THAT OF POTASSIUM

Interest in the biological properties of rubidium and cesium stems from their close physicochemical relationship to potassium. Reference to the Periodic Table shows these elements to be adjacent members of the Group I alkali metal series, which has the order: lithium, sodium, potassium, rubidium, cesium. In terms of their chemical behavior the elements of this series may be separated into two groups, the division falling between sodium and potassium. Potassium, rubidium, and cesium display very similar electrical, chemical, and physical properties, which differ only quantitatively in a well-defined manner. When considered in this context, a comparison of the biological behavior of these ions can provide much important information to the investigator concerned with the mechanisms handling the alkali metals in the living organism. A study of the comparative biochemistry of rubidium and cesium is therefore an excellent, although indirect, method for investigation of the normal biochemistry of potassium.

The purpose of this paper is to review briefly certain aspects of the physiology of rubidium and cesium with particular reference to their relation to potassium. Space does not permit a complete or detailed discussion of this subject, and some active fields of investigation have been arbitrarily omitted. Emphasis has been chiefly placed on those topics most pertinent to mammalian, or at least vertebrate, physiology; newer developments in certain areas with which the author has had some personal experience have received greatest attention.

ANALYSIS OF K, Rb, AND Cs MIXTURES

The close chemical similarity of these ions gives rise to serious analytical problems. Flame spectrophotometry may be satisfactorily adapted to the analysis of certain mixtures of cesium and potassium,[61] but the close proximity of their spectral lines makes the analysis of mixtures of rubidium and potassium by this method a more complicated problem. Nevertheless, it has

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been reported that accurate determinations of rubidium in the presence of potassium have been carried out, using standard solutions containing appropriate concentrations of potassium.[9, 50] Most of the standard gravimetric or titrimetric methods capable of separating sodium from potassium do not separate potassium from rubidium and cesium. Thus, for example, precipitation as chloroplatinate, which will give accurate estimations of potassium in the presence of sodium, will not distinguish between potassium and its sister elements, rubidium and cesium.[37] Mixtures of these elements may be satisfactorily separated, however, by the use of paper chromatography,[78] or by ion exchange chromatography.[13, 14] Qualitative analyses of mixtures are probably most efficiently carried out by spectrographic techniques, but interfering effects of one ion on another make accurate quantitative analysis difficult.

When it is necessary only to measure rubidium or cesium in the presence of potassium, in a system not originally containing the former ions, labelling with radioisotopes offers a simple and satisfactory solution. Suitable isotopes of both elements are available. Rb^{86} has a half-life of 19 days, while the half-life of Cs^{134} is two to three years and that of Cs^{137} is 33 years; all three may be detected by their gamma radiation. In short-term experiments potassium may be analyzed simultaneously by K^{42} labelling, provided that the circumstances permit the attainment of a constant specific activity before cesium or rubidium is added to the system. The counting of samples containing K^{42} and one of the rubidium or cesium isotopes is accomplished by allowing the short-lived K^{42} (half-life 12 hours) to decay before the rubidium or cesium is counted. A satisfactory technique for experiments in which K^{42} cannot be used is to combine a chemical method with the radioisotope technique.[80] The total concentration of potassium and rubidium or potassium and cesium is measured by titration of chloroplatinate,[15] and the rubidium or cesium concentration is determined from the radioactivity. Potassium is then calculated by difference.

DISTRIBUTION IN THE ENVIRONMENT AND IN LIVING TISSUES

Of the Group I alkali metals, sodium and potassium are found in the earth's crust in the greatest abundance. The concentration of each is approximately 2.5 per cent by weight. The percentage of rubidium in the earth is roughly 1/2500th that of potassium or sodium, while the concentration of cesium is only 1/10th that of rubidium.[22] Spectrographic analysis has revealed rubidium to be present in virtually all animal tissue in the range of from 2×10^{-3} to 6×10^{-3} per cent (of dry weight),[7, 71] whereas tissue concentrations of potassium are usually some 300-800 times greater

than this. It is thus apparent that the abundance of rubidium relative to potassium is significantly greater in living tissues than in the terrestrial environment. Early spectrographic studies failed to identify cesium in animal tissues, but more recently this element has been found in the retinal tissue of various farm animals[67] and in the carcasses of a great variety of vertebrate species.[5] The average tissue concentration of cesium is reported to be about 3×10^{-3} per cent of dry weight.

The distribution in the body of naturally occurring rubidium resembles that of potassium, in that both elements are found in relatively high concentrations in red cells, muscle tissue, and viscera, with much less in bone and plasma.[6,7,71] No data are available on the distribution of cesium. However, tracer doses of radioactive rubidium[36,49,84] and cesium[27,88] have been found to distribute themselves in the body with a pattern quite similar to that of the naturally occurring rubidium. All plant and animal cells studied so far have been found freely permeable to these ions. The permeability rates observed have varied considerably with the particular cell and the circumstance but are in general comparable to those for potassium.[10,16,20,45,65,72,79] When fed to animals in large quantity, rubidium is only slowly excreted in the urine[41,54] and accumulates to a considerable degree in muscle and in most other soft tissues with a distribution similar to that of naturally occurring potassium or rubidium.[54,55]

GENERAL PHYSIOLOGICAL EFFECTS

The physiological similarity between potassium and its chemical cousins, rubidium and cesium, was probably first noted by Ringer in 1882,[63] when he observed that the action of rubidium on the contractions of the isolated frog heart was almost identical with that of potassium. The effects of cesium were like those of potassium in some aspects, but the similarity between rubidium and potassium was much closer. In numerous investigations since then this general relationship has been demonstrated for a great variety of biochemical and physiological processes.[31] These include, for example, such diverse actions as the ability of these ions to neutralize the toxic action of lithium on fish larvae,[47] their effects on the motility of spermatazoa,[58] and the influence of varying extracellular ionic concentrations on the resting potentials in isolated nerve[21,25,32] and muscle[66] preparations and on the configuration of the electrocardiogram.[39,75,76] A similar relationship also exists with respect to the activating effects of the alkali metal ions on the release of acetylcholine by respiring brain tissue,[53] the utilization of Krebs cycle intermediates by isolated mitochondria,[57] the fermentation capacity of yeast,[48,65] the active transport of sodium by frog skin,[34] and on the behavior

of isolated enzyme systems.[35, 82] Potassium and rubidium are often very nearly interchangeable, but cesium, although it resembles potassium more closely than sodium or lithium, is never a physiological substitute for potassium.

To the extent that rubidium or cesium are capable of substituting for potassium in biochemical and biophysical processes one would expect that these ions would be at least a temporary nutritional substitute for potassium. Thus, it has been shown that rubidium and, to a lesser extent, cesium can replace potassium as an essential nutrient for the growth of bacteria,[51, 52] yeast,[42] sea urchin eggs,[46] and rats.[24, 80] Young rats immediately cease growing on a potassium-free but otherwise adequate diet and usually die within a few weeks. The addition of rubidium to the diet will permit almost normal growth to occur for one or two weeks before the animals sicken again and die. To a more limited degree cesium is also capable of substituting for potassium in this way.[24, 55] Characteristic lesions develop in the kidneys and in the skeletal and cardiac muscles of potassium-depleted animals.[23] The addition of rubidium or cesium to the diet will prevent these changes[24] and if they have already developed, the feeding of these elements will rapidly effect a cure.[61]

ACID-BASE METABOLISM

Potassium depletion produced by diets low in potassium often results in marked changes in the acid-base balance of extracellular and intracellular fluid. There is evidence to suggest that loss of potassium from tissues is accompanied by migration of hydrogen ions from extracellular to the intracellular spaces, thereby increasing the acidity of tissues while producing an extracellular alkalosis.[18] The usual renal response to extracellular alkalosis would be expected to result in a diuresis of bicarbonate with subsequent restoration of plasma bicarbonate concentration to normal levels. With loss of intracellular potassium, however, the renal threshold for bicarbonate is increased as the result of accelerated exchange of hydrogen in tubular cells for sodium in the glomerular filtrate.[4] This increased threshold for bicarbonate prevents the excretion of the extracellular bicarbonate, and the urine remains relatively acid.

The administration of potassium to rats with diet-induced potassium-depletion and extracellular alkalosis corrects the acid-base disturbance chiefly at the tissue level by the restoration of normal tissue composition and the extrusion of hydrogen from cells back into the extracellular fluid.[18, 58] It has been shown recently that a similar displacement of intracellular hydrogen probably also occurs with the administration of rubidium

to normal or potassium-depleted animals, but the acidifying effects of rubidium can be even more pronounced than those of potassium.[59] The difference between potassium and rubidium is most marked in intact animals and least evident in nephrectomized animals. This suggests that the kidney is at least partly responsible for the acidosis.

Balance studies on normal intact rats loaded with rubidium or potassium support this suggestion for they demonstrate a significant reduction in ammonia excretion of the rubidium-loaded animals.[41] Simultaneously, these animals become much more acidotic than the controls which have been loaded with potassium. The cause of the suppression of ammonium excretion by rubidium remains to be elucidated. It is not apparently a function of urine pH because this was essentially unaffected in both groups; nor can it be attributed to any direct effect of rubidium on glutaminase activity, since *in vitro* studies with renal homogenates fail to demonstrate enzyme sensitivity to wide variations in rubidium or potassium concentration.[62] Tissue bicarbonate concentration is low in slices of rat kidney cortex depleted of potassium, and it is restored to normal by adding either potassium, rubidium, or cesium to the medium.[1] Consequently, there is no reason to believe that the ammonia effect is mediated through large differences in pH inside the renal tubular cells.

When administered to normal animals, cesium produces a milder degree of acidosis than does rubidium.[60] Like rubidium, however, it is capable of correcting the alkalosis associated with potassium depletion. No data are yet available on the effect of cesium on renal ammonia production.

RENAL EXCRETION

Considerable evidence supports the concept that the renal excretion of potassium is accomplished by tubular secretion of this ion in exchange for sodium in the filtrate.[3] There is also some reason to believe that tubular secretion of hydrogen occurs through a similar pathway and that, under some circumstances at least, tubular secretion of hydrogen and potassium are "competitive" processes.[4]

Initial studies on the renal clearance of rubidium carried out with tracer doses of Rb^{86} indicated that the clearance of rubidium was usually slightly less than that of potassium and tended to vary concordantly with the excretion of potassium under a variety of stimuli.[58] More recently, simultaneous potassium and rubidium clearances have been measured during the infusion of rubidium loads. In these experiments the rapid infusion of rubidium into normal dogs resulted in progressive elevation of plasma potassium and an increase in the excretion of potassium and rubidium. The excretion of

potassium during the administration of rubidium was slightly more rapid than during the administration of potassium loads which produced the same elevation of plasma potassium concentrations. Although the mean ratio of rubidium to potassium clearance was approximately 0.85, this ratio varied from .3 to 1.8. The ratio of rubidium to inulin clearance (C_{Rb}/C_{In}) varied from .2 to 2, without any definite relationship to plasma rubidium level. Demonstrable secretion of rubidium, arbitrarily defined as a C_{Rb}/C_{In} ratio greater than 1.10, occurred in at least 15 periods in four dogs.* It was always accompanied by still greater secretion of potassium and was observed following the administration of large doses of Diamox as well as occasionally during the slow infusion of rubidium into animals previously prepared by chronic loading of potassium. Further evidence for the tubular secretion of rubidium was afforded by an experiment in which the administration of BAL following the injection of a mercurial diuretic was observed to increase the excretion of rubidium as well as that of potassium. All these facts suggest that rubidium and potassium share the same renal transport mechanism. The differences between the rate of excretion of the two ions could be explained on the basis of a slower rate of secretion of rubidium by distal tubular cells.

Tracer doses of cesium in the dog are cleared at rates only about half that of potassium, and the excretion of cesium does not vary concordantly with the potassium excretion.[77] No studies on the excretion of cesium loads have yet appeared, and nothing is known of the transport mechanisms involved.

TISSUE ACCUMULATION

Earlier work had indicated clearly that animal tissues were capable of accumulating large amounts of rubidium or cesium.[30, 54, 55] More than half of the total tissue potassium content was replaced by rubidium when the latter was added to a low potassium diet.[30] It has recently been shown that most of the intracellular potassium of frog muscle can be replaced by rubidium or cesium if the tissue is allowed to soak in potassium-free Ringer solution to which rubidium or cesium has been added.[50] Experiments with tracer doses of radioactive rubidium[36, 49, 50] and cesium[88] in intact animals have shown that muscle tissue, red cells, and most viscera are capable of accumulating these ions against tissue-plasma concentration gradients equal to or greater than those existing for potassium.

*Since there is no evidence of any binding of rubidium to dog plasma proteins,[40] the rate of filtration of rubidium can be estimated as the product of the plasma level and the inulin clearance.

In a series of experiments in which potassium-depleted, alkalotic young rats were fed equivalent mixtures of potassium and rubidium or potassium and cesium for periods of two to three weeks it was found that considerably higher concentration gradients were established for the rarer alkali metals than for potassium.[80] Up to two-thirds of intramuscular potassium was displaced by rubidium or cesium. Final intracellular/extracellular ratios for potassium remained normal and unaltered at approximately forty to one, but the ratio for rubidium was approximately three times this value while the ratio for cesium was roughly 4½ times the potassium value. It would thus appear that skeletal muscle of the rat accumulates these cations at equilibrium in a definite order of preference: cesium>rubidium>potassium.

The relationship described above between renal transport of rubidium and potassium could be explained in terms of this relative "preference" for rubidium in renal tubular cells. The rise in clearance of potassium produced by rubidium infusions could thus be due to displacement of potassium from secreting cells by rubidium. The relatively lower clearance of rubidium compared to potassium would then be a reflection of the relative tenacity with which rubidium maintains its intracellular position and resists exchange for sodium in the glomerular filtrate.

The observations on the relative uptake of the alkali metals have a critical bearing on some current concepts of ion transport in muscle cells. It was at first postulated that the accumulation of potassium was explained by a Gibbs-Donnan equilibrium resulting from the virtual impermeability of the normal muscle cell membrane to the influx of sodium and the efflux of the large intracellular anions.[8] When it subsequently became clear that the membrane was in fact quite permeable to sodium, the theory was modified to include the idea that sodium is actively extruded from muscle by an energy-requiring "pump," and that potassium accumulates as a result of the outward transport of sodium.[17, 19, 38, 74]

The potential difference generated by this continuous "sodium pump" is thought to provide an electrical field for the inward movement of potassium. Potassium is therefore conceived as moving into cells *against* a chemical gradient, but *down* the electrical gradient, the net result involving no change in electro-chemical potential and, hence, no active transport of this ion. Recent observations of ion transport by the isolated frog skin lend credence to this view, for they demonstrate that this preparation, at least, possesses an active transport system for sodium (and not for potassium) which is entirely responsible for the maintenance of a potential difference across the skin.[81]

If the above view were correct, one would expect similar concentration gradients at equilibrium for potassium, rubidium, and cesium, since they would be diffusing passively along the same electrical field. The large differences in gradient actually observed with these three ions therefore constitute a strong argument against this theory. Although it is conceivable that different mechanisms are involved in the transport of each of these ions, the existence of a single process is strongly suggested not only by the close chemical similarity of the ions but also by the fact that each ion of the group appears to competitively inhibit the penetration of the other two into frog muscle.[45] Thus, the simplest and most reasonable conclusion would seem to be that a single process is responsible for the cellular accumulation of all three and that this process cannot be simply passive diffusion.

If the "passive diffusion" theory is not valid for muscle, then at least two alternatives seem possible. The first is that in addition to the active outward transport of sodium there is also an active inward transport system for which these ions compete, the order of selectivity being Cs>Rb>K. This idea gains indirect support from recent studies with yeast,[17, 64] green algae,[68] and desheathed toad nerve fibers,[69] which indicate the existence of an active inward transport system for potassium which can operate without the simultaneous efflux of sodium. No direct support for the active and independent uptake of potassium by muscle has yet appeared, but several lines of evidence indicate that simultaneous movements of sodium and potassium are not always in stoichiometrical reciprocity, as might be expected if potassium accumulation depended upon a sodium pump.[17, 18, 70] Finally, there is evidence to suggest that potassium uptake by human erythrocytes is an active process, although it has not yet been demonstrated to be independent of sodium efflux.[28, 29] The kinetics of rubidium and cesium transport in red cells suggest that both these ions are handled by the same process responsible for active uptake of potassium, and they appear to compete with potassium for entrance into the cell.[13, 72]

A second alternative to the passive diffusion theory of potassium uptake is suggested by the analogy between the relative accumulation of the alkali metals by muscle tissue and the behavior of certain ion exchange resins, which selectively bind these ions in the same order of preference.[9] Selective binding of cations by fixed negative charges inside the cell has been proposed as a mechanism for the normal accumulation of intracellular potassium.[44] This hypothesis gains some support from the recent observation that relatively high concentrations of potassium are apparently maintained in frog muscle which has been soaked in potassium-free Ringer solution and poisoned with cyanide plus iodoacetate.[70] On the other hand, selective bind-

ing of cations within the cell would result in significant reductions in tissue osmotic activity as intracellular potassium is displaced by cations like rubidium or cesium for which the fixed negative charges have a higher affinity.[26] The absence of any evidence of water shifts in these experiments[60] therefore indicates either that large-scale binding does not occur, or that there exist cellular mechanisms which maintain total osmotic constancy despite fluctuations in cation activity.

At present there is no experimental basis for a choice among these or any other alternatives to the passive diffusion theory of potassium uptake. Obivously, much more information is required before an adequate description of ion transport in muscle cells can be given. It might safely be predicted, however, that similar or identical mechanisms are probably involved in the uptake of potassium, rubidium, and cesium. An explanation of the preferential accumulation of rubidium and cesium would for this reason contribute much toward the ultimate solution of the ion transport problem.

USE OF RUBIDIUM FOR DETERMINATION OF "POTASSIUM SPACE"

It has been suggested that because of its similar distribution in tissues, Rb^{86}, or small amounts of nonradioactive Rb^{85}, might be used instead of K^{42} in the determination of total exchangeable potassium or in the study of various aspects of potassium metabolism.[2,13] If this were so, use of Rb^{86} might offer considerable practical advantages over K^{42} because the former has a half-life of some 19 days, while the half-life of K^{42} is only 12½ hours. However, the observations discussed above indicate clearly that neither rubidium nor cesium can be used interchangeably with potassium for tracer studies, because tissues establish considerably higher concentration gradients for the two heavier elements than for potassium. One would expect that values for exchangeable potassium based on the ratios $\frac{Rb^{86}}{K^{39}}$ or $\frac{Cs^{137}}{K^{39}}$ in urine or blood would be spuriously high. A recent comparison of the "exchangeable" potassium calculated from the distribution of K^{42} and of Rb^{86} confirms this prediction, in that the Rb^{86} space was found to be significantly larger.[36]

TOXICITY

Although rubidium and cesium are capable of substituting for potassium in many biochemical processes, organisms will not tolerate indefinite replacement of potassium by either of these ions. Growing rats fed large quantities of rubidium or cesium, with or without the addition of potassium

to their diet, begin to show signs of toxicity within a few weeks, and eventually they all die.[24, 30, 61] No specific histological lesions are noted. The obvious manifestations of toxicity are chiefly in the neuromuscular sphere, with the animals usually becoming progressively more irritable and finally dying in convulsions. It is not yet clear how many of these symptoms are due to the acidosis usually produced by the administration of rubidium and cesium,[59] but preliminary experiments suggest that acidosis is not necessary to the development of toxicity.[60] Altered neuromuscular reactivity resulting from the profound changes in intracellular cation composition probably is an important factor, but more information is required before this question can be settled.

The acute toxic effects of rubidium infusions in the dog appear to be produced chiefly by the action of this ion on the electrical activity of the heart. Infusion of rubidium, which results in progressive elevation of plasma rubidium and potassium levels, produces a definite sequence of electrocardiographic changes which resemble in many ways the effects of hyperpotassemia alone.[39, 75] Thus, for example, when the plasma rubidium is 4 mEq./L and the potassium concentration is the same, one may observe peaking of T-waves which is quite comparable to the effect of elevating potassium concentration to 8 mEq./L. However, the presence of rubidium causes frequent ventricular extrasystoles and a reduction in amplitude of the S-wave, neither of which effects is seen regularly with infusions of potassium alone. Another difference between rubidium and potassium is revealed by the fact that dogs infused rapidly with rubidium die with ventricular fibrillation when the plasma concentrations of rubidium and potassium have each risen to levels of approximately 5 to 6 mEq./L, giving a total rubidium plus potassium concentration somewhat lower than the concentrations of potassium alone which produce fatal cardiotoxicity in animals infused with potassium.

These differences are probably explained by effects of rubidium on membrane potentials. It has been shown that the threshold potential of isolated myocardial fibers is decreased, and their spontaneous irritability usually augmented by a marked increase in potassium content of the bathing solution.[21] This effect is commonly assumed to be the result of a reduction in the concentration ratio $\left(\frac{K\ in}{K\ out}\right)$ term in the Nernst equation for the resting potential. The changes in the distribution of potassium caused by rapid infusion of rubidium might be expected to have a greater effect on myocardial irritability than would be predicted simply from the rise in serum potassium because the concentration of intracellular potassium is being

reduced simultaneously with the rise in extracellular concentration. The direct influence of the intra- and extracellular rubidium ions on the membrane potential is not known. If the tendency for rubidium ions to migrate out of cells was significantly less than that of potassium, replacement of some intracellular potassium by rubidium would tend to reduce the resting potential and thus perhaps contribute to the electrocardiographic changes observed.

SUMMARY AND CONCLUSIONS

This brief review of the physiology of rubidium and cesium has indicated some of the evidence for the close similarity of the biological effects of these ions to those of potassium. However, significant quantitative differences have been noted between the physiological behavior of these ions; cells do distinguish between them, and higher organisms will not indefinitely tolerate substitution of rubidium or cesium for potassium. Future attempts to explain the differences in the biological behavior of these ions in terms of their known physicochemical relationships should contribute much to an understanding of the biological systems involved. It may be suggested, for example, that the ultimate explanation of the mechanism underlying the preferential accumulation of rubidium and cesium by muscle tissue will probably reveal the nature of the process normally responsible for potassium uptake. The evidence available at present strongly suggests that this process is not a matter of simple diffusion.

The extent to which muscle tissues accumulate the "foreign" ions, rubidium and cesium, to the exclusion of potassium raises some interesting speculation. It seems clear that potassium owes its normal position as the chief intracellular cation solely to its relative abundance in the earth's crust. Were rubidium and cesium more abundant, there is every reason to believe that they, rather than potassium, would be the chief cations of muscle tissue. What consequences this would have had for the evolution of life is hard to imagine. In view of the toxicity of the heavier alkali ions it is apparent that the development of higher forms in an environment more rich in rubidium or cesium would have been contingent upon successful adaptation to the presence of these elements in the cell fluid.

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